Remarks

This Preliminary Amendment is substantially the Amendment After Final submitted May 10, 2005 in response to the then-pending final Office Action, except that claims 1 and 9 have since been amended. The Examiner, in an Advisory Action dated May 25, 2005, indicated that the amendments in the Amendment After Final would not be entered.

The specification has been amended at paragraphs 0011, 0025, 0039, 0041, 0053, 0058, 0059, 0060, 0066, 0089, 0112, 0410, 0412, 0453, 0461 and 0471 to correct typographical errors, references to certain figures, and syntax. No new matter is added.

Claims 1-5, 8-14, 16-18, 22, 23, 37, 38, 41 and 42 are currently pending in the application. Applicant thanks the Examiner for deeming claims 22, 23, 41 and 42 to be allowable. Claims 1, 3, 9, 16, 17 and 37 are currently amended. Claims 4 and 38 are canceled without prejudice. Applicant expressly reserves the right to prosecute the subject matter of canceled claims 4 and 38 in this or a related application. New claims 43 and 44 are added. Support for new claim 43 is found in the specification as published at least at paragraphs 0060 (referring to FIG. 25B); 0447 (COS cells transfected with apo-4 detectably expressed apo-4 proteins on the cell surface); 0454 (Apo-4 appears to exist as a cell-surface heterodimer). Support for new claim 44 is found in the specification as published at least in paragraphs 0124, 0405-0411 (apo-4 cDNA in vectors CDM8 and pIG1Fc) and 0425 (apo-4 cDNA fragment in pBluescript SK+). Upon entry of the present amendments, claims 1-3, 5, 8-14, 16-18, 22, 23, 37 and 41-44 will be pending in this application.

Claim 1 is amended to recite that the claimed polynucleotide is a fragment of SEQ ID NO:2, wherein said fragment of SEQ ID NO:2 comprises nucleotides 710-996 of SEQ ID NO:2, or the complement of said polynucleotide. Support for this amendment is found in FIGS. 1, 1A, 1B and 2, and in the specification at paragraphs 0098-0110. Claim 1 is also amended to include the complement of the claimed polynucleotide. As the complement of a nucleotide sequence is inherent in the sequence, no new matter is added by this amendment. Claim 3 is amended to recite that the claimed polynucleotide codes for a protein or polypeptide the binds to a polynucleotide having the sequence of SEQ ID NO: 2. Support for the amendment to claim 3 is found in the specification as published at paragraphs 0052, 0053 and 0442. Claim 9, dependent from claim 1, is amended. Support for this amendment is found at least in FIGS. 1, 1A, 1B and 2, and in the specification at paragraphs 0098-0110. Claim 14 is amended to replace "nucleic acid" with the more accurate "polynucleotide." Claim 16, is amended to delete reference dependent from claim 1, is amended to delete the phrase "or to SEQ ID NO: 1," which was rendered superfluous by the amendment to claim 1. Claim 17 has been amended to recite that

the claimed cell is an isolated cell. Support for amended claim 17 is found in the published specification at least at paragraphs 0124, and 0447 (COS cells transfected with apo-4 detectably expressed apo-4 proteins on the cell surface). Finally, claim 37 has been amended to recite that the particular conditions treated are muscular dystrophy and leukemia. Support for amended claim 37 is found in the published specification at least at originally-filed claims 38 and 40; and at paragraphs 0052, 0053, 0118, 0123 and 0442.

With respect to new claims 43 and 44, Applicant submits that, because claim 43 recites an inherent property of SEQ ID NO: 2, and because claim 44 only additionally states that the polynucleotide of claim 1 is contained within a vector, no new search of the prior art need be performed.

It is submitted that no new matter has been introduced by the present amendments and new claims and entry of the same is respectfully requested.

The Rejections of Claims 1-5, 8-14, 16-18 and 37-38 Under 35 U.S.C. § 112, First Paragraph Should be Withdrawn

The Examiner has rejected claims 1-5, 8-14, 16-18 and 37-38 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description and enablement requirements. The Examiner contends that the specification discloses only a single variant of SEQ ID NO: 2 containing the polynucleotides of SEQ ID NO: 1 or variant thereof, and that this disclosure is not sufficient to support claims directed to SEQ ID NOS: 1 or 2, and variants thereof. Applicant traverses.

Applicant first notes that the Examiner appears to believe that the claimed polynucleotides must encode a protein that binds to CD33 (*see, e.g.*, Office Action, page 3, lines 3-4 and 21-24; page 4, lines 2-4, 13-15; etc.). While CD33 played a role in the discovery of apo-4, as described in the specification, Applicant respectfully points out that the claimed and disclosed polynucleotides may also be used as, for example, probes to determine the presence of leukemic cells, or to may be used to construct primers that amplify PCR products that include the inversion breakpoint. Thus, the recited and claimed polynucleotides need not produce a polypeptide that binds CD33 in order to be adequately described and enabled.

Applicant also notes that the Examiner refers several times to "functional equivalents" or "functional variants" of the claimed polynucleotides (*see, e.g.*, page 5, line 8; page 8, lines 11, 21). Applicant respectfully reminds the Examiner that claim language directed to "substantial functional equivalents" of the claimed polynucleotides was deleted in the amendments in the response to the Office Action mailed May 10, 2004.

Applicant has amended claim 1 to recite that the claimed polynucleotide comprises "a fragment of SEQ ID NO:2, wherein said fragment of SEQ ID NO:2 comprises nucleotides 710-996 of SEQ ID NO:2, or the complement of said polynucleotide." Thus, the claimed polynucleotides are all present within the sequence of SEQ ID NO: 2, and are therefore adequately described and enabled. Applicant submits that this amendment overcomes the rejection of claim 1 on this basis. Likewise, Applicant submits that this amendment overcomes the rejection of claims 2, 5 and 8 on this basis, as all are dependent from claim 1.

Applicant has canceled claim 4, thus mooting the Examiner's rejection of this claim on this basis.

Claim 9, as amended, is directed to a regulatory DNA sequence comprising nucleotides 710 to 996 of SEQ ID NO:2, or a fragment of nucleotides 710 to 996 of SEQ ID NO:2 comprising nucleotides 850-996 of SEQ ID NO:2. Claim 9 as amended is sufficiently described in the specification as follows. The sequence of 710 to 996 of SEQ ID NO:2 (referred to in the specification as SEQ I D NO: 1B), or a fragment of nucleotides 710 to 996 of SEQ ID NO:2 comprising nucleotides 850-996 of SEQ ID NO:2 (referred to in the specification at SEQ ID NO: 1A), is shown in FIGS. 1A, 1B and FIG. 2. The use of these polynucleotides as regulatory sequences is described in the Detailed Description of the Invention at paragraphs 0101-0109. Additionally, the Examples (*see* para. 0442-0444) describe an experiment in which the 3′ 287 nucleotides of the apo-4 cDNA (*i.e.*, the sequence corresponding to SEQ ID NO: 1B) was removed (para. 0442). While the full-length apo-4 cDNA (SEQ ID NO: 2) produced 40 and 50 kDa polypeptides in *in vitro* transcription, the cDNA lacking SEQ ID NO: 1B produced no polypeptides (not simply shorter polypeptides). Paragraphs 0483-0484 propose that the inversion sequence (SEQ ID NO: 1) operates as a bi-directional enhancer, indicating that expression of a sequence, particularly a nucleotide sequence comprising one or more stop codons, would be modified if the claimed polynucleotide were placed either 5′ or 3′ to the sequence to be expressed. Moreover, as an enhancer, the claimed polynucleotide would not necessarily need to comprise a promoter, etc. in order to act as a regulatory element.

Further, the construction of vectors and expression cassettes, and the expression of such sequences, is well-known in the art. *See.*, *e.g.*, Sambrook *et al.*, *Molecular Cloning - A Laboratory Manual, 2nd Edition*, Cold Spring Habour Laboratory Press, New York (1989). A person of skill in the art, therefore, would know which nucleotide sequences claim 9 encompasses, and would be able to determine straightforwardly which would be of the most use. *See also Ex parte Friedberg*, Appeal No. 2004-2314 (B.P.A.I. 2005) (overturning Examiner's

nonenablement rejection of claims to SEQ ID NO: 2 and SEQ ID NO: 4 (both polypeptides), and specific fragments thereof, where antibodies had been generated only to the full-length sequences; "The enablement requirement is met if the description enables any mode of making and using the invention," *quoting Johns Hopkins Univ. v. CellPro Inc.*, 152 F.3d 1342, 1361, 47 U.S.P.Q.2d 1705, 1714 (Fed. Cir. 1998)). Thus, Applicant believes that claim 9, and claims 10-13, dependent from claim 9, are adequately described an enabled.

With respect to claim 14, Applicant clarifies that the claimed polynucleotide is intended to detect the apo-4 sequence), that is, the particular dystrophin variant containing the inversion sequence (SEQ ID NO: 1) as described in the present specification. To this end, the polynucleotide comprises a "compris[es] an inversion start site of apo-dystrophin-4" (*i.e.*, as indicated in FIG. 6), and "a first plurality of nucleotides [that] hybridizes 5′ to said inversion strt site" and "a second plurality of nucleotides [that] hybridizes 3′ to said inversion start site," ensuring that the claimed polynucleotide will hybridize to both sides of the inversion start site, which is a principal feature defining the apo-4 nucleotide sequence. The claimed polynucleotides are described at least in FIGS. 1A, 1B and 2, and are useful for the detection of leukemic cells (*see, e.g.*, paragraphs 0122-0123). The identification of polynucleotides suitable for hybridization to specific sequences, and that are capable of differentiating sequences (*e.g.*, apo-4 and normal dystrophin) are well-developed in the art and, through the use of computer programs, quite routine. Applicant respectfully submits, therefore, that the polynucleotides of claim 14 are adequately described and enabled.

With respect to claim 17, Applicant has, per the Examiner's suggestion, amended the claim to recite "an isolated cell." Applicant respectfully submits that this amendment removes the Examiner's rejection of this claim on these bases.

Finally, with respect to claims 37 and 38, Applicant has canceled claim 38, and has amended claim 37 to recite a pharmaceutical composition for the treatment of leukemia or muscular dystrophy. Claim 37 is directed to a pharmaceutical composition containing the polynucleotide of claim 1; claim 1 is, as Applicant has explained above, adequately described and enabled as amended. The specification teaches that the nucleotide sequences of the invention may be used to treat conditions resulting from protein truncation, *e.g.*, leukemia and muscular dystrophy. *See* paragraphs 0118, 0123. In fact, the pharmaceutical composition may comprise a complementary, antisense apo-4 sequence to use to decrease apo-4 polypeptide expression. *See* paragraphs 0123, 0484 (stating that the 5′ 453 nucleotides of apo-4 are likely an oncogene the expression of which is facilitated by the 3′ end of the apo-4 sequence. The polynucleotide in the claimed pharmaceutical composition need not interact with, or affect

CD33. The formulation of nucleic acids into pharmaceutically-acceptable compositions is well-known. The delivery and expression of nucleic acid sequences into, for example, muscle tissue, is known. *See, e.g.* Walter *et al.*, "Noninvasive Measurement of Gene Expression in Skeletal Muscle," *Proc. Natl. Acad. Sci. U.S.A.* 97(10):5151-5155 (2000), a copy of which was attached to the previous Amendment; *see also* Wolff *et al.*, "Direct Gene Transfer Into Mouse Muscle *in Vivo*," *Science* 23:247(4949 Pt 1):1465-8 (1990). Thus, the polynucleotides contained within the claimed pharmaceutical composition are themselves described, as is their relationship to leukemia and muscular dystrophy, and the formulation of such pharmaceutical compositions is well-known in the art. As such, Applicant submits that claim 37, as amended, is enabled.

Applicant therefore respectfully requests that the Examiner withdraw the rejection of the claims on these bases.

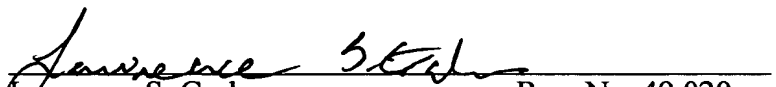
CONCLUSION

Applicant respectfully requests that the above amendments and remarks be entered in the present application file. An early allowance of the present application is respectfully requested. Should the Examiner have any concerns as to the allowability of any pending claim, or has concerns that any claim, as amended, would require further search, the Examiner is invited to contact the undersigned at 858-314-1171 or 858-314-1200 to discuss the matter to facilitate allowance of the application.

No fee, other than the extension of time fee, is believed due for this Amendment. However, if a fee is due, please charge such fee to Jones Day Deposit Account No. 50-2468.

Respectfully submitted,

Date: September 12, 2005



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